

THE BERLIN DECLARATION ON TUBERCULOSIS AND ITS CONSEQUENCES FOR TB RESEARCH AND CONTROL IN THE WHO-EURO REGION

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In his famous presentation ‘Ueber Tuberculose,’ Robert Koch (1843–1910) changed the view on tuberculosis as disease, identified *Mycobacterium tuberculosis* as the etiologic agent and revolutionized the fight against infectious disease in diagnosis, therapy and prevention. Koch gave this presentation in Berlin on March 24, 1882 [1]. Exactly 100 years later, 1982, the International Union Against Tuberculosis and Lung Disease (IUATLD) proposed the 24th of March as ‘World Tuberculosis Day’. Fourteen years later, in 1996, the World Health Organization (WHO) confirmed this day as the official day commemorating the disease and its victims, as well as the global endeavours to fight tuberculosis.

Keywords: tuberculosis, World Tuberculosis Day, Berlin Declaration on Tuberculosis, Koch–Metschnikow-Forum

Introduction

In contrast to Robert Koch's expectations, the time between 1882 and today could not be used to substantially reduce the global burden of tuberculosis disease [2]. Progress in diagnostics, treatment and prevention of tuberculosis was rather limited and did not result in efficiently fight the disease.

Diagnostics

Based on Koch's discoveries, microscopic diagnostics of acid-fast stained mycobacteria was developed for sputum analysis – it is still today the gold standard in diagnosing the pathogen in potential tuberculosis (TB) patients. Koch's tuberculin served as the basis for a skin test, revealing contact of the immune system to mycobacteria, but today a promise of a more precise immunological diagnosis can be obtained with the aid of two blood tests using *Mycobacterium tuberculosis*-specific antigens. However, skin and blood tests provide no information on whether a contact to mycobacteria/*M. tuberculosis* resulted in latent or active tuberculosis disease or even complete clearance of the pathogen from the host. Microbiological diagnosis of TB is the main tool in successfully fighting the disease globally. In recent years, diagnostic advances have been achieved through improved cell culture techniques of *M. tuberculosis* and utilizing advanced molecular biology techniques to detect bacterial DNA in clinical specimens. Moreover, these techniques are often combined to accu-

rate identify *M. tuberculosis*, as well as obtain vital information on drug sensitivity and resistance [3].

Therapy

Therapeutic intervention for TB patients is difficult, and progress has been more inadequate than in diagnostics. After the discovery of the principles of chemotherapy, streptomycin was the first drug found to be effective against *M. tuberculosis*. Streptomycin monotherapy failure was followed by the launch of more anti-TB drugs in the 1950s and 60s. Since then, there has been no new development of ‘first line’ drugs dedicated primarily to TB treatment. As multidrug resistance (MDR) evolved, second line drugs were identified to act as the last line of defence against the spread of MDR-TB. MDR- and extremely drug resistant (XDR) TB are now spreading faster than ever and soon, there will be virtually no effective anti-TB drugs available [2, 4, 5]. Currently, a few new drug candidates are in the production pipeline. However, much of their chemistry and pharmacology are based on already established functional mechanisms and thus have the increased potential to rapidly lose their efficacy.

Prevention

Robert Koch's tuberculin, originally developed as vaccine candidate, turned out to be ineffective. *Mycobacterium*

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bovis BCG, a live vaccine, was introduced in the 1920s and is now the most widespread vaccine ever applied to mankind. Unfortunately, there is still an increase in new infections every year and currently about 1.6 million patients die from TB each year [6]. Prevention through a new vaccine candidate is essential, and potential new candidates are increasing and will be clinically tested (actual overview in [7]). Vaccine trials, however, have a major drawback in that the efficacy of the vaccine candidate will be proven only after decades and only if protection of a vaccinated population can be shown. Evidence of protection by biomarkers would shorten this clinical study time tremendously, but up to now, there have been no reliable biomarkers to be used in a TB vaccine setting [3, 5].

The current global TB situation is alarming

In 1993, the World Health Organization (WHO) declared TB a global health emergency, since incidence and prevalence numbers significantly increased during the past years. Since then, many attempts have been undertaken to globally fight the TB pandemic, without measurable success. Two world regions are mainly affected by TB: Sub-Saharan Africa and the WHO-Euro region. Both regions struggle against complicating problems: in the African region, TB–HIV comorbidity is the predominant obstacle to a successful containment of the disease. *M. tuberculosis* and HIV potentiate each other in furthering the clinical diseases. In the WHO-Euro region, the emergence of MDR significantly reduces the treatment success rate [8]. In the past years, we observe the appearance of MDR-TB in Africa and a growing HIV/AIDS epidemic in the successor states of the former Soviet Union. Thus, treatment and epidemiological containment of TB grows more complicated [5, 9].

In order to address the increasing challenges in fighting TB within the WHO-Euro region, the WHO and the German Federal Ministry of Health organized a Ministerial Forum on TB in Berlin in October 2007. From 53 member states, 49 sent their health ministers, prime ministers or other high representatives to Berlin. At the end of the forum, the Berlin Declaration on Tuberculosis was adopted by the present ministers [10, 11]. The declaration names the main problems in containing TB in the WHO region, calls upon the member states to increase their involvement in TB control and lists self-commitments of high- and low-burden countries. At the end, it is stated that progress in fighting TB should be evaluated every two years [11].

In order to scientifically prepare the Ministerial Forum and at the same time to commemorate the 125th anniversary of Robert Koch's groundbreaking presentation 'Ueber Tuberculose,' the Koch–Metschnikow-Forum (KMF) together with other TB organizations in Germany organized a scientific symposium on the occasion of World Tuberculosis Day in March 2007. The results of the symposium formed the basis of the discussion preparing the declaration. In turn, the Berlin Declaration on Tuberculosis is still today the basis of all activities for the KMF in TB research and control in bilateral scientific projects with partners in Eastern Europe and Central Asia.

As the first scientific symposium on World Tuberculosis Day was successful, KMF decided to organize symposia every year in March on the occasion of World TB Day.

The following scientific symposia were organized by KMF on the occasion of World TB Day:

Year	Main focus
2007	125th anniversary of Robert Koch' lecture 'Ueber Tuberculose'; preparation of the upcoming Ministerial Forum and the Berlin Declaration in Oct. 2007
2008	Current status of research in diagnostics, treatment and prevention of TB
2009	Public Health issues of tuberculosis control
2010	Exchanging expertise: Problems and challenges in Sub-Saharan Africa and the WHO-Euro Region
2011	Childhood Tuberculosis
2012	Evaluating the progress five years after the Berlin Declaration on Tuberculosis; festive symposium on the occasion of the 75th birthday of Prof. H. Hahn, the president of KMF

Every single scientific symposium of KMF at World TB Day referred to the Berlin Declaration, even if the main focus of the symposium was different. All symposia were organized by KMF together with representatives of the WHO-Euro office, and some symposia were used to officially launch WHO reports on different subjects in TB control, such as the report on MDR-TB.

KMF promoted the Berlin Declaration also at the World Health Summit (WHS, www.worldhealthsummit.org), which is organized by Charité University Medicine and its partners of the M8 Alliance every year in Berlin in October 2009, at the first World Health Summit, and a symposium was organized by KMF focusing on the evaluation of the progress made two years after the Ministerial Forum. The main topic of this symposium was HIV–TB comorbidity [10]. Two years later, at the third WHS 2011, the evaluation of the progress made was presented with a political focus. The symposium on World TB Day 2012 focused on the scientific evaluation and its epidemiological and Public Health outcomes (s.a., table with World TB Day symposia).

In order to avoid that the Berlin Declaration on Tuberculosis will not end up as just a well-printed document containing non-committal ideas to stop TB, KMF will continue organizing symposia, conducting studies in Eastern Europe and providing the political platform to develop and employ strategies to stop TB in the WHO-Euro region. The scientific symposia on the occasion of World Tuberculosis Day will constitute the backbone of these activities.

References

1. Gradmann C: Robert Koch and the white death: from tuberculosis to tuberculin. *Microbes Infect* 8(1), 294–301 (2006)
2. Migliori GB, Loddenkemper R, Blasi F, Raviglione MC: 125 years after Robert Koch's discovery of the tubercle bacillus: the new XDR-TB threat. Is 'science' enough to tackle the epidemic? *Eur Respir J* 29(3), 423–427 (2007)
3. McNerney R, Maeurer M, Abubakar I, Marais B, McHugh TD, Ford N, Weyer K, Lawn S, Grobusch MP, Memish Z, Squire SB, Pantaleo G, Chakaya J, Casenghi M, Migliori GB, Mwaba P, Zijenah L, Hoelscher M, Cox H, Swaminathan S, Kim PS, Schito M, Harari A, Bates M, Schwank S, O'Grady J, Pletschette M, Ditui L, Atun R, Zumla A: Tuberculosis diagnostics and biomarkers: needs, challenges, recent advances, and opportunities. *J Infect Dis* 15, 205 Suppl 2, S147–158 (2012) Epub 2012 Apr 10
4. Nicolau I, Ling D, Tian L, Lienhardt C, Pai M: Research questions and priorities for tuberculosis: a survey of published systematic reviews and meta-analyses. *PLoS One* 7(7), e42479 (2012)
5. Raviglione M, Marais B, Floyd K, Lönnroth K, Getahun H, Migliori GB, Harries AD, Nunn P, Lienhardt C, Graham S, Chakaya J, Weyer K, Cole S, Kaufmann SH, Zumla A: Scaling up interventions to achieve global tuberculosis control: progress and new developments. *Lancet* 379(9829), 1902–1913 (2012). Erratum in: *Lancet* 16, 379(9833), 2242 (2012)
6. Ulrichs T: Immunology of tuberculosis and current status of vaccine development. *Pneumologie* 62(3), 143–147 (2008)
7. Ottenhoff TH, Kaufmann SH: Vaccines against tuberculosis: where are we and where do we need to go? *PLoS Pathog* 8(5), e1002607 (2012)
8. Marx FM, Skachkova EI, Son IM, Strelis AK, Urazova OI, Hahn H, Krämer A, Ulrichs T: Control of tuberculosis in Russia and other countries of the former Soviet Union. *Pneumologie* 63(5), 253–260 (2009)
9. Lienhardt C, Glaziou P, Uplekar M, Lönnroth K, Getahun H, Raviglione M: Global tuberculosis control: lessons learnt and future prospects. *Nat Rev Microbiol* 10(6), 407–416 (2012)
10. Castell S, Hauer B, Manissero D, Ulrichs T, Zaleskis R, Loddenkemper R: Berlin declaration on tuberculosis: high level follow-up of high priority countries for TB control in the WHO-EURO region 'Double Trouble or Double Success? Bringing Together Diseases and Programs' – A symposium report. *Pneumologie* 64(7), 422–429 (2010)
11. WHO-Euro Office: The Berlin Declaration on Tuberculosis. www.euro.who.int/document/e90833.pdf; last access: Sept. 7, 2012